UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte LARS WIKLUND, TORBJORN KARLSSON, and ANDERS NORDGREN

Appeal No. 2007-3912
Application No. 09/773,394
Technology Center 1600

Decided: November 19, 2007

Before TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

The Appellants appeal the Examiner's final rejection of claims 1-2 and 4-21.

We have jurisdiction under 35 U.S.C. § 6(b) (2006).

Representative claim 1 reads as follows:

1. A method of preserving bodily protein stores in a catabolic patient, comprising the concomitant and separate administration of a pair of pharmaceutical agents consisting essentially of (a) a first composition containing at least one of α-ketoglutarate and α-ketoglutaric acid and being devoid of ammonium, and (b) a second composition containing ammonium and being devoid

of a α-ketoglutarate and α-ketoglutaric acid, the amounts of the pair being effective to preserve skeletal muscle, wherein any composition administered containing at least one of α-ketoglutarate and α-ketoglutaric acid is devoid of ammonium.

Cited References

Vinnars	US 5,310,768	May 10, 1994
Veech	US 5,719,119	Feb. 17, 1998
Bollish	US 5,219,330	Jun. 15, 1993

Taconic "Sprague Dawley Outbred Rats," http://www.taconic.com/anmodels/sprague.htm

Grounds of Rejection

Claims 1-2 and 4-21 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of compliance with the written description requirement (new matter).

Claims 1-2 and 4-21 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Claims 1-2 and 4-21 stand rejected under 35 U.S.C. § 103 for obviousness over Veech and Vinnars in view of Taconic and Bollish.

DISCUSSION

Background

> Glutamine is one of the predominant amino acids in the body and constitutes more than 50 % of the total intracellular free amino acid pool in skeletal muscle. It is utilised mainly as an energy source and nitrogen carrier. During postoperative and posttraumatic catabolism its availability is decreased. This results in depletion of skeletal muscle glutamine and, with continued utilisation of glutamine by the intestine, also to low blood glutamine levels. α-Ketoglutarate (α-KG), the biologic precursor of glutamine, has been tried in human enteral and parenteral nutrition. In clinical studies, parenteral and enteral administration of α-KG was claimed to prevent severe muscle protein breakdown . . . , and to promote mucosal repair in the small intestine

> … and wound healing. . . . Glutamine turnover after trauma, sepsis or surgery is characterised by muscle protein catabolism and concomitant draining of the muscular free glutamine store to meet the increasing demand of fast dividing cells, e.g. enterocytes, immune cells and fibroblasts. During acidosis and starvation, the liver participates in pH homeostasis by switching from urea to glutamine synthesis. . . . This is achieved by a decreased periportal utilisation of bicarbonate in the urea cycle, leaving ammonium (NH_4^+) available for perivenous hepatic glutamine synthesis.
>
> Ammonium is occasionally administered to patients in the form of a pharmacologically acceptable salt such as the chloride in spite of ammonium being considered neurotoxic in that high concentrations is known to be neurotoxic. . . . In skeletal muscle, about 50% of arterial ammonium content is metabolised. . . . The amination of α-KG by glutamate dehydrogenase produces glutamate from which, catalysed by glutamine synthetase through the addition of one amide group, glutamine is formed.
>
> The administration of glutamine and/or small peptides comprising glutamine residues to a patient being in a state of glutamine depletion thus is a less than direct way of coping with such deficiency since glutamine is poorly soluble in water and cannot be sterilised by autoclavation while dipeptides are costly. A more direct way of preserving or raising blood glutamine levels thus is highly desirable.

(Specification 1-2.)

"It is an object of the present invention to provide an improved method for preserving body protein stores in a patient being in a catabolic state by inducing endogenous synthesis of glutamine." (Specification 3.)

Written Description

Claims 1-2 and 4-21 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of compliance with the written description requirement (new matter).

The Examiner contends that

> the application provides no support for "composition containing at least one of alpha-ketoglutarate and alpha-ketoglutaric acid and ***being devoid*** of ammonium," "composition containing ammonium and ***being devoid*** of a alpha-ketoglutarate and alpha-ketoglutaric acid," "wherein any composition administered containing at least one of alpha-ketoglutarate and a-ketoglutaric acid is devoid of ammonium. [sic]" in claim 1, and "pharmaceutical composition comprising at least one of alpha-ketoglutarate and alpha-ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium," "pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and being devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid" in claim 15.
>
> Further, claim 1 as currently amended, require[s] "concomitant and ***separate"*** administration. The application as originally filed lacks support for ***"separate"*** administration.

(Answer 3-4.)

Appellants argue there is support in the Specification for separate and concomitant administration of a composition containing ammonium and being devoid of α-ketoglutarate and α-ketoglutaric acid at page 12, lines 10-16. We agree with Appellants and find that the Specification, page 12, lines 10-22 provides support for the language of pending claim 1. In particular, the Specification describes an experiment in which an infusion of NH_4Cl mixed with saline (devoid of α-ketoglutarate) is given to eight animals, and a separate infusion of α-ketoglutaric acid dissolved in normal saline (devoid of ammonium) is also administered to the eight animals.

In view of the above, the rejection of the claims for lack of written description (new matter) is reversed.

Indefiniteness

Claims 1-2 and 4-21 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

The Examiner contends that

> Claim 1 recites ***"concomitant and separate*** administration." The phrase is confusing in that [sic] how the administration is carried out concomitantly and separately. The specification or the claims provide no further clarification as the meaning of "concomitant and separate administration." The claim is indefinite as to how the administration is carried out.

Appellants argue that according to their plain, "everyday" meanings, the term "concomitant" means "to accompany," and the term "separate" means that "the two compositions are not present in a single composition." (Br. 7.) We find Appellants' definitions to be consistent with Specification, page 12, lines 10-22, wherein two separate infusions of NH4CL and α-KGA are given at the same time (concomitantly).

As set forth in *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.,* 927 F.2d 1200, 1217 (Fed. Cir. 1991):

> The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits.").

Furthermore, claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure

as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971).

When the terms "concomitant" and "separate" are given their ordinary meaning, and when they are read in the context of page 12 of the Specification, we do not find the claim meaning to be indefinite or inconsistent with their ordinary usage. The rejection of the claims for indefiniteness is reversed.

Obviousness

Claims 1-2 and 4-21 stand rejected under 35 U.S.C. § 103 for obviousness over Veech and Vinnars in view of Taconic and Bollish. We select claim 1 as representative of the rejection before us since Appellants have not separately argued the claims. 37 C.F.R. 41.37(c)(1)(vii).

The Examiner argues that

> Veech (USPN 5,719,119) teaches a parenteral nutrition solution comprising carboxylic metabolite anions, such as lactate and/or alpha-Ketoglutarate, (0.1 - 150 mMole/L) and cation such as ammonium and sodium (0.1-150 mMole/L), See, particularly, columns 5. Particular examples comprising alpha-ketoglutarate and ammonium is disclosed. [S]ee Table 9, col. 20, examples 1.4-1.5. . . . Veech further teaches that post-traumatic or post-operative patients suffer from a negative nitrogen balance, col. 7, line 55 to column 8 line 7. . . .
>
> Vinnars (USPN 5,310,768) teaches a method of treatment of post operative and Post-traumatic patients for improving glutamine content in skeletal muscle and preventing the reduction of protein synthesis capacity, hence also, improve the nitrogen balance and even make it positive by administering alpha-ketoglutarate, alone or in combination with other actives, see col. 2, lines 54-63 and abstract in particular.

(Answer 6-7.)

Taconic is relied on for the disclosure of the body weight of Sprague Dawley rats and Bollish is relied on to show conventional intravenous infusion rates. (Answer 7-8.) The Examiner acknowledges that "Veech and Vinnars do not . . . teach the administration of two separate compositions." (Answer 7.)

The Examiner finds, however, that

> it would have been obvious to one of ordinary skill in the art at the time the invention was made to [make] a dosage unit, wherein alpha-ketoglutarate and/or alpha-ketoglutaric acid, and ammonium are present separately in two composition[s], but are ready for the concomitant administration for preserving bodily protein, because both alpha-ketoglutarate and ammonium are known to be useful in methods of treating post-operative/post-traumatic patients and normalizing/preserving skeletal muscle glutamine/nitrogen content. Concomitant administration of the two agents which are known to be useful to improve nitrogen balance and preserve skeletal muscle individually into a single composition useful for the very same purpose is prime facie obvious. See In re Kerkhoven 205 USPQ 1069.

(Answer 7-8.)

We conclude that the Examiner has provided sufficient evidence to support a prima facie case of obviousness of the method of claim 1. Veech discloses the intravenous administration of a single composition containing alpha-ketoglutarate (α-KG) and ammonium as a form of parenteral nutrition to prevent negative nitrogen balance. (Veech, col. 7, ll. 57-65, col. 20, ll. 25-63.) Vinnars describes a method for improving glutamine content in skeletal muscle by administering alpha-ketoglutarate alone or with other actives. (Vinnars, col. 2, ll. 54-64.) We agree with the Examiner that it would have been obvious to administer the components of Veech's composition (Veech, col. 20, Table 9) as two or more separate compositions.

Veech teaches that "[a]dministration of solutions of amino acids alone, without simultaneous administration of one or another substrate couple with which that amino acid is in a state of near equilibrium, results in a change of the cellular redox state towards that state which is characteristic of the starved state." (Veech, col. 9, ll. 10-15.) Veech teaches the redox pair of [NH_4^+] [alpha ketoglutarate $^{2-}$] [1-glutamate $^{1-}$] at col. 14, ll. 40-50. Each of the components of the redox pair are known to be useful, in combination, for the same purpose, to prevent negative nitrogen balance. The prior art of Vinnars indicates that alpha-ketoglutarate can be administered alone to prevent negative nitrogen balance. (Answer 10.) Thus, the prior art suggests that alpha-ketoglutarate can be administered alone to prevent negative nitrogen balance, and because the components of the redox pair of [NH_4^+] [alpha ketoglutarate $^{2-}$] [1-glutamate $^{1-}$] together are required to prevent a starved state leading to negative nitrogen balance, one of ordinary skill in the art would have been motivated to administer the other components of the redox pair together with alpha ketoglutarate, either in the same composition or in two separate compositions, concomitantly with alpha-ketoglutarate.

"[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious" the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

Furthermore,

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it

> is likely the product [is] not of innovation but of ordinary skill and common sense.

KSR, 127 S. Ct. at 1742.

In the present case, the prior art identifies predictable solutions within the technical grasp of the ordinary artisan, i.e., that both α-ketoglutarate and ammonium together are useful in a parenteral solution to prevent negative nitrogen balance. Thus, we find that the concomitant and separate administration of a pair of pharmaceutical agents consisting essentially of (a) a first composition containing at least one of α-ketoglutarate and α-ketoglutaric acid and being devoid of ammonium, and (b) a second composition containing ammonium and being devoid of a α-ketoglutarate and α-ketoglutaric acid, the amounts of the pair being effective to preserve skeletal muscle, wherein any composition administered containing at least one of α-ketoglutarate and α-ketoglutaric acid is devoid of ammonium, would have been obvious to one of ordinary skill in the art.

We further agree with the Examiner that the record provides no evidence that the separate infusions of the claimed compounds provide unexpected results or are actually better than a single infusion with respect to therapeutic efficacy. (Answer 10.)

Appellants argue that, "the inventors found that infusion increased arterial glutamine concentration in a dose dependent fashion when the ammonium load was increased and the dose of α-KG was kept constant but not when the α-KG load was increased and the dose of ammonium was kept constant." (Br. 8-9.) However, Appellants' evidence is not commensurate in scope with the pending claims. Appellants do not claim a method of administering two separate compositions wherein the ammonium load is

increased and the dose of α-KG is kept constant. Therefore, we are not persuaded by Appellants' argument.

Appellants ask, "[i]f the metabolite anion α-KG is present in the composition of the Veech for the purpose of avoiding metabolic acidosis, why would one employ a separate administration of a material such as ammonium which is known to cause metabolic acidosis when so administered?" (Br. 9.) The answer to this question is provided by Veech which teaches that "[a]dministration of solutions of amino acids alone, without simultaneous administration of one or another substrate couple with which that amino acid is in a state of near equilibrium, results in a change of the cellular redox state towards that state which is characteristic of the starved state." (Veech, col. 9, ll. 10-15.) Veech teaches the redox pair of [NH_4^+] [alpha ketoglutarate $^{2-}$] [1-glutamate $^{1-}$] at col. 14, ll. 40-50.

Appellants also ask the corollary that, "[i]f the presence of both α-KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria, why would one [compound] be omitted?" (Br. 10.) Appellants argue that Veech provides no motivation to separate the components of a redox pair. (Br. 10.) However, Appellants do not omit administration of one of the redox pairs, they merely administer each component of the pair separately and at the same time as the opposing member of the redox couple. As discussed above, we have found that it would have been obvious to administer the components of Veech's composition (Veech, col. 20, Table 9) as two or more separate compositions. Thus, we are not persuaded by Appellants' arguments.

After evidence or argument is submitted by the Appellant in response to an obviousness rejection, "patentability is determined on the totality of the record, by

a preponderance of evidence with due consideration to persuasiveness of the argument." *In re Oetiker*, 977 F.2d 1443, 14454 (Fed. Cir. 1992).

We find a preponderance of the evidence in this case supports a finding of obviousness of the claimed invention and the obviousness rejection is affirmed.

CONCLUSION

The rejection of claims 1-2 and 4-21 under 35 U.S.C. § 112, first paragraph, for lack of compliance with the written description requirement (new matter) is reversed. The rejection of claims 1-2 and 4-21 under 35 U.S.C. § 112, second paragraph, for indefiniteness is reversed. The rejection of claims 1-2 and 4-21 under 35 U.S.C. § 103 for obviousness over Veech and Vinnars in view of Taconic and Bollish is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

lbg

Edward A Meilman
Dickstein Shapiro Morin & Oshinsky LLP
1177 Avenue of the Americas 41st Floor
New York NY 10036-2714